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Mini Review

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The Mitochondrial Interactome in Alzheimer's Diseases

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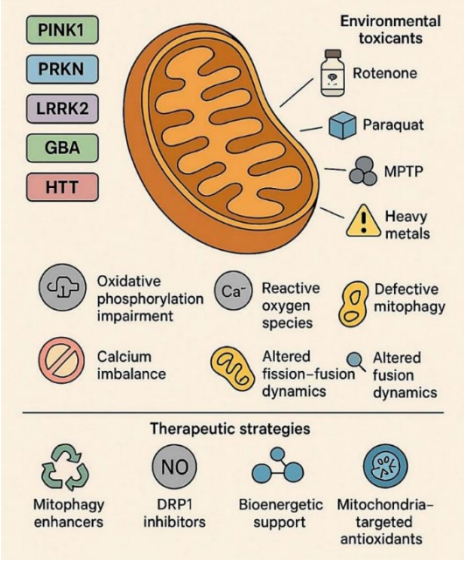
Abstract

Mitochondrial dysfunction is a central driver of neurodegeneration in Alzheimer's disease (AD) and Huntington's disease (HD). This review synthesizes evidence on the convergence of genetic mutations and environmental toxicants on mitochondrial pathways to promote pathology and critically evaluates emerging mitochondria-targeted therapies. We highlight the impact of mutations in genes such as PSEN1, PSEN2, APP, TREM2, and HTT, alongside exposures to agents such as rotenone, paraquat, heavy metals, and solvents, in disrupting mitochondrial integrity. Key mechanisms include impaired oxidative phosphorylation, calcium dysregulation, reactive oxygen species accumulation, defective mitophagy, and altered fission–fusion dynamics. We further emphasize the synergistic interplay between genetic vulnerability and environmental insults, positioning the mitochondrial interactome as a unifying framework for understanding AD and HD pathogenesis. We assess therapeutic strategies, such as mitophagy enhancers, dynamin-related protein 1 inhibitors, and mitochondria-targeted antioxidants, while highlighting significant translational challenges, including poor brain penetrance and variable patient responses. Finally, we propose a precision medicine approach, leveraging patient-derived induced pluripotent stem cells, advanced imaging modalities, and multi-omics biomarker discovery to facilitate early detection and individualized interventions. By integrating mechanistic, toxicological, and therapeutic perspectives, this review underscores the pivotal role of mitochondria and identifies them as a promising target for disease-modifying therapies in AD and HD.

Keywords: Neurodegenerative diseases, Alzheimer's disease, Huntington's disease, Mitochondrial interactome, Mitophagy, Environmental toxins

Introduction

Neurodegenerative disorders such as Alzheimer's disease (AD) and Huntington's disease (HD) are progressive and debilitating conditions characterized by selective neuronal loss and central nervous system dysfunction.[1] Despite distinct genetic etiologies and clinical presentations, both diseases share a central pathological hallmark: mitochondrial dysfunction. As central hubs of energy metabolism, redox regulation, calcium buffering, and cell death signaling, mitochondria are particularly critical for neurons, which have high metabolic demands and limited regenerative capacity.[2,3] Early studies of mitochondrial involvement in neurodegeneration focused on discrete processes such as deficits in adenosine triphosphate (ATP) production or increased oxidative stress.[4] However, it is now clear that mitochondria do not operate in isolation but are dynamically regulated by a complex network of genetic, environmental, and intracellular signals.[5] This network, referred to herein as the mitochondrial interactome, encompasses both intrinsic factors, such as mutations in nuclear and mitochondrial genes, and extrinsic influences, including exposure to neurotoxicants and inflammation.[6] Disruptions to this tightly regulated system can trigger a cascade of pathological events, ultimately leading to neuronal injury and death.[7]



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In AD, mutations in genes such as PSEN1, PSEN2, and APP disrupt key aspects of mitochondrial quality control, including calcium homeostasis, redox balance, and mitochondrial dynamics.[8] These genetic vulnerabilities are exacerbated by environmental toxins and factors such as heavy metals and air pollutants, which can inhibit mitochondrial respiratory complexes and potentiate oxidative stress.[9-12] Similarly, in HD, the expanded Cytosine–Adenine–Guanine trinucleotide (CAG) repeat in the HTT gene produces a mutant huntingtin protein, which disrupts mitochondrial trafficking, oxidative phosphorylation, and calcium handling.[13] Although environmental links in HD are less well defined than in AD, accumulating evidence suggests that factors such as metal exposure, stress, and dietary deficiencies may modulate disease progression via mitochondrial pathways.[3]

Moreover, mitochondrial dysfunction in AD and HD extends beyond organellar defects to include impaired signaling, biogenesis, proteostasis, and inter-organelle communication. These disruptions collectively compromise cellular energy homeostasis, exacerbate excitotoxic and inflammatory stress, and promote the accumulation of toxic proteins. Mitochondria thus serve as both sensors and amplifiers of neuropathological stress, integrating genetic susceptibilities and environmental exposures.[9] This review aims to integrate current knowledge on how genetic mutations, environmental toxicants, and mitochondrial signaling pathways converge in the pathogenesis of AD and HD. By framing neurodegeneration through the lens of the mitochondrial interactome, we seek to highlight shared molecular mechanisms, identify potential therapeutic targets, and propose new directions for precision medicine approaches in neurodegenerative disease management.

Beyond mitochondrial impairment, environmental toxins disrupt other cellular systems that contribute to neurodegeneration. Several pesticides and heavy metals can induce ER stress, triggering the unfolded protein response and perturbing calcium homeostasis, which further sensitizes neurons to apoptotic signaling.[101] Toxins such as dieldrin have been shown to impair lysosomal function and autophagic flux, exacerbating mitophagy deficits already present in PINK1- and Parkin-mutant backgrounds. Chronic exposure to airborne pollutants (PM2.5, PAHs) and manganese also activates microglial inflammatory cascades, leading to sustained release of pro-inflammatory cytokines (e.g., Tumor Necrosis Factor Alpha (TNF-α), Interleukin-1 Beta (IL-1β)) and reactive oxygen species.[102,103] This neuroinflammatory milieu not only damages neurons directly but also amplifies ER and mitochondrial stress, establishing a vicious cycle of cellular dysfunction.[104] These findings underscore that the pathogenic synergy between genetic predisposition and environmental exposure extends beyond mitochondria to include ER stress responses, lysosomal degradation pathways, and neuroinflammatory signaling. Together, these interconnected dysfunctions accelerate the progression of PD and HD.

Therapeutic targeting of mitochondrial dysfunction in PD and HD

Given the central role of mitochondrial dysfunction in the pathogenesis of both PD and HD, mitochondria have emerged as critical therapeutic targets (Fig.5a,b).[105] Unlike traditional symptomatic treatments, which primarily modulate neurotransmitter levels, mitochondrial-targeted therapies aim to reverse or mitigate upstream cellular pathology, offering the potential for disease modification.[106] A key therapeutic strategy involves restoring mitophagy—the selective autophagic degradation of dysfunctional mitochondria—which is compromised in PD due to mutations in PINK1 and Parkin, and in HD due to mHTT-mediated inhibition of autophagic flux.[107] Several pharmacological agents are being developed to enhance PINK1-Parkin signaling or bypass defective steps.[108] For instance, small molecules such as KTP601 can stabilize PINK1 on the outer mitochondrial membrane, while others mimic phosphorylated ubiquitin to activate Parkin. AMP-activated protein kinase activators like metformin and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) have been shown to stimulate both mitophagy and mitochondrial biogenesis in preclinical PD models, even with impaired PINK1-Parkin signaling. Despite strong preclinical data, translating these findings has proven challenging. Mitophagy enhancers and metabolic modulators often face significant hurdles, such as poor pharmacokinetics, uncertain dosing regimens, and variable target engagement in human neurons, which have limited their clinical advancement.[109–111] Another therapeutic axis involves modulating mitochondrial dynamics—specifically, correcting the imbalance between fission and fusion.[112] Excessive fission, common in both PD and HD, contributes to bioenergetic decline and pro-apoptotic signaling. Pharmacological inhibitors of DRP1, such as Mdivi-1, can reduce mitochondrial fragmentation and preserve neuronal viability.[113] In HD models, enhancing the expression of fusion-promoting proteins like MFN2 and OPA1 through gene therapy or small molecules has shown promise in restoring mitochondrial morphology and improving ATP production.[114] However, Mdivi-1 and related DRP1 inhibitors have not progressed to human trials due to off-target effects and safety concerns, underlining the difficulties in developing safe modulators of mitochondrial dynamics.[115,116] At the genetic level, CRISPR/Cas9 technologies are being employed to correct the pathogenic HTT expansions or to knock down hyperactive mutant LRRK2 alleles. These approaches have successfully restored mitochondrial respiration and dynamics in patient-derived iPSC models, presenting a promising avenue for precision thera

peutics.[117]

Figure created using Biorender and Napkin AI. (a) Therapeutic Strategies: Emerging mitochondria-targeted interventions address these pathological mechanisms. Approaches include restoring mitophagy (KTP601, NAD+ precursors), modulating mitochondrial dynamics (Mdivi-1, MFN2 activators), enhancing redox balance (MitoQ, SkQ1, SS-31), and improving bioenergetics (Coenzyme Q10, SS-31). Together, these strategies highlight mitochondria as a central therapeutic target in neurodegenerative disease modification. (b) Pathophysiological Basis: Mitochondrial dysfunction contributes to neuronal vulnerability in PD and HD through several interconnected pathways: impaired mitophagy, altered dynamics, redox imbalance, and compromised bioenergetics. These disruptions amplify oxidative stress, energy failure, and progressive neurodegeneration. ATP, adenosine triphosphate; HD, Huntington's disease; MFN2, mitofusin 2; NAD+, nicotinamide adenine dinucleotide (oxidized form); OPA1, optic atrophy 1; PD, Parkinson's disease; ROS, reactive oxygen species.

Improving mitochondrial bioenergetics remains a cornerstone of therapeutic development. Agents such as coenzyme Q10 and creatine, though showing mixed results in large-scale trials, have demonstrated the ability to enhance electron transport chain activity and buffer ATP levels in early-stage PD and HD, as shown in Figure 5a.[118] More recently, targeting NAD+ metabolism with compounds like nicotinamide riboside and nicotinamide mononucleotide has gained attention. These compounds boost sirtuin activity and PGC-1α-mediated biogenesis, thereby enhancing mitochondrial resilience to oxidative and metabolic stress. However, translating these strategies has proven challenging. Large-scale clinical trials of coenzyme Q10 and creatine in PD and HD yielded disappointing results, showing no significant disease-modifying benefits despite strong biochemical rationale and early pilot data. These failures highlight challenges related to brain penetrance, trial design, and the possibility that mitochondrial rescue may only be effective during specific disease stages or in particular genetic subgroups.[119–122] Mitochondria-targeted antioxidants represent another promising avenue.[123] Unlike conventional antioxidants, compounds such as MitoQ, SkQ1, and SS-31 are designed to accumulate within mitochondria, where they neutralize ROS at the source and stabilize mitochondrial membranes. These molecules have shown promise in reducing lipid peroxidation and preserving mitochondrial potential in animal models and are currently undergoing clinical evaluation.[119,124,125] Parallel strategies involve activating Nrf2 pathway—a master regulator of antioxidant and detoxification responses. Nrf2 activators like dimethyl fumarate upregulate cellular defenses and improve mitochondrial morphology and function in both PD and HD models. While early-phase trials are ongoing, their long-term efficacy and safety remain uncertain. These translational gaps underscore the need for precision medicine approaches, integrating patient-derived iPSCs, multi-omics biomarkers, and advanced imaging to identify patients most likely to benefit from mitochondria-targeted therapies.[25,126]

Cutting-edge approaches such as mitochondrial transplantation and nanomedicine represent the next frontier. Mitochondrial transplantation involves the direct transfer of healthy mitochondria into damaged neurons, a strategy that has shown neuroprotective effects in rodent models of PD.[127] Complementarily, nanocarrier systems, including liposomes and cerium oxide nanoparticles, are being engineered to deliver antioxidants, gene-editing tools, or even intact mitochondria across the blood–brain barrier. While challenges remain concerning immune compatibility, targeted delivery, and long-term integration, these novel platforms underscore a future in which mitochondria-centric interventions may transform the therapeutic landscape of neurodegenerative diseases.[117]

Limitations and future directions

Despite significant advances, important gaps remain in understanding the mitochondrial interactome in neurodegeneration. Mechanistic connections between specific gene mutations (e.g., PINK1, PRKN, LRRK2, GBA, and HTT) and mitochondrial dysfunction are still incompletely mapped, particularly across different neuronal subtypes. Human data on long-term epigenetic consequences of environmental exposures are scarce, and standardized biomarkers for mitochondrial dysfunction are lacking, hindering both early diagnosis and therapeutic monitoring. Furthermore, most evidence derives from PD and HD models, which may not fully represent mitochondrial dynamics in other neurodegenerative diseases such as Alzheimer's disease or ALS. Future research should focus on (i) patient-derived iPSC models and advanced imaging modalities to capture disease heterogeneity, (ii) multi-omics approaches to discover reliable, clinically translatable mitochondrial biomarkers, (iii) integrative studies that assess the combined impact of genetics, environment, and organelle cross-talk (ER stress, lysosomal impairment, neuroinflammation), and (iv) translational efforts to improve brain penetrance and specificity of mitochondria-targeted therapeutics. Collaborative, cross-disease studies will be crucial to validate the mitochondrial interactome as a unifying framework and accelerate the development of precision therapies.

Conclusions

This review positions mitochondria at the center of PD and HD pathogenesis, where genetic mutations and environmental exposures converge to disrupt cellular homeostasis.

By mapping the mitochondrial interactome, we identify actionable therapeutic nodes, including impaired mitophagy, fission–fusion imbalance, and oxidative stress, that represent actionable therapeutic nodes. Promising strategies that move beyond symptomatic management include mitochondria-targeted antioxidants (e.g., MitoQ, SS-31), DRP1 inhibitors (e.g., Mdivi-1), NAD+ boosters (e.g., nicotinamide riboside, nicotinamide mononucleotide), and gene-editing techniques for mutations in genes such as LRRK2 and HTT. Combining these approaches with precision medicine tools—such as iPSC-based modeling, advanced imaging, and biomarker-guided patient stratification—will be essential to overcome translational barriers. Mitochondria represent not only a shared vulnerability in PD and HD but also a promising focal point for therapeutic development. Harnessing mechanistic insights into the mitochondrial interactome can pave the way for individualized, mitochondria-centered interventions with the potential to alter disease progression and improve patient outcomes.

Authors' contributions

Study concept and design (JW, SC), acquisition of data (JW), analysis and interpretation of data (JW, SC), drafting of the manuscript (JW), critical revision of the manuscript for important intellectual content (JW, SC, MR), framing and refinement of specific sections (MR), visualization including design and preparation of figures (JW, SC), and study supervision (SC, MR). All authors have made significant contributions to this work and have approved the final manuscript.

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